Enhancing proteasomal processing improves survival for a peptide vaccine used to treat glioblastoma.

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Public Summary:
Using the immune system for cancer therapy is an exciting approach that has produced impressive results in several hard to treat tumors. Anti-cancer vaccines have the potential to be the most effective immunotherapy, but further improvement is needed. For glioblastoma, the most common but also most deadly brain tumor, we discovered a tumor specific protein called EGFRvIII. This was used to develop a vaccine that in clinical trials has shown some success in treating glioblastoma but a stronger immune response is needed. The proteasome is a molecule that processes vaccines in our cells. We thought that if we could enhance processing by the proteasome then this might increase the effectiveness of the vaccine. By studying variations in the sequence of the vaccine, we improved processing and greatly improved survival over the original vaccine in a mouse model. Using new technology that we developed, we then isolated the processed products from the proteasome. In turn, we showed that these proteasome products were also effective vaccines. These are important results because we show how to make a vaccine more potent and how to isolate the active components that might further improve vaccination. These principles could be applied to any vaccine and we have already found important proteasome products from the SARS-CoV-2 virus.

Scientific Abstract:
Despite its essential role in antigen presentation, enhancing proteasomal processing is an unexploited strategy for improving vaccines. pepVIII, an anticancer vaccine targeting EGFRvIII, has been tested in several trials for glioblastoma. We examined 20 peptides in silico and experimentally, which showed that a tyrosine substitution (Y6-pepVIII) maximizes proteasome cleavage and survival in a subcutaneous tumor model in mice. In an intracranial glioma model, Y6-pepVIII showed a 62 and 31% improvement in median survival compared to control animals and pepVIII-vaccinated mice. Y6-pepVIII vaccination altered tumor-infiltrating lymphocyte subsets and expression of PD-1 on intratumoral T cells. Combination with anti-PD-1 therapy cured 45% of the Y6-pepVIII-vaccinated mice but was ineffective for pepVIII-treated mice. Liquid chromatography-tandem mass spectrometry analysis of proteasome-digested pepVIII and Y6-pepVIII revealed that most fragments were similar but more abundant in Y6-pepVIII digests and 77% resulted from proteasome-catalyzed peptide splicing (PCPS). We identified 10 peptides that bound human and murine MHC class I. Nine were PCPS products and only one peptide was colinear with EGFRvIII, indicating that PCPS fragments may be a component of MHC class I recognition. Despite not being colinear with EGFRvIII, two of three PCPS products tested were capable of increasing survival when administered independently as vaccines. We hypothesize that the immune response to a vaccine represents the collective contribution from multiple PCPS and linear products. Our work suggests a strategy to increase proteasomal processing of a vaccine that results in an augmented immune response and enhanced survival in mice.